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Neoadjuvant Chemotherapy in 126 Operable Breast Cancers

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126 patients with non-inflammatory operable breast cancer, who otherwise would have undergone modified radical mastectomy (MRM), were treated by induction chemotherapy. Before treatment, every patient had a local and general assessment, and pathological or cytological evidence of malignancy. Patients received, every 3 weeks, the same treatment with doxorubicin, vincristine, cyclophosphamide, 5-fluorouracil (AVCF); methotrexate was added in 80 cases (AVCFM). Tumour shrinkage greater than 50% was documented in 105 (83%) of the 126 women. A higher objective response rate was obtained in aneuploid or high S phase tumours, especially in the patients treated with methotrexate. After chemotherapy, 41 patients were then treated by radiotherapy alone after complete or subcomplete response; 64 had a residual tumour that could be treated by conservative surgery and radiotherapy. Only 19 had MRM and radiotherapy. Histopathological complete remission was documented in 1 case; isolated residual tumour cells were found in 5 patients. Thus primary chemotherapy enhanced the possibility of breast conservation in up to 83% of the cases in a series in which most would have been otherwise subjected to a MRM because of tumour size.
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INTRODUCTION

NEOADJUVANT CHEMOTHERAPY is supposed to have at least the same effect on distant metastasis prevention as an adjuvant treatment with the same regimen. The aim of this timing of chemotherapy is to reduce the tumour size before surgery, resulting in a lower rate of total mastectomy.

Anthracycline-based combinations appear to be a treatment of choice in first line chemotherapies for breast cancer. Among them, FAC (5-fluorouracil, doxorubicin, cyclophosphamide) and its homologue with epirubicin, FEC, have been widely used, resulting in a median survival of about 18 months for metastatic patients in most papers [1]. AVCF (doxorubicin, vincristine, cyclophosphamide, 5-fluorouracil) is very similar; with the same drugs, administered for 4–5 days every 4 weeks, resulting in a higher dose intensity for 5-fluorouracil and cyclophosphamide. This treatment led, in our experience with metastatic patients, to a median survival of at least 2 years. We have been using this protocol for several years in adjuvant situations [2, 3]. For 47 node-positive premenopausal patients, overall survival was about 80% at 3420 days, with 65% of these patients still being in complete remission; these results were significantly better than those of 26 patients treated with CMF (oral cyclophosphamide, methotrexate, 5-fluorouracil) [3]. With neoadjuvant use of AVCF in 110 inflammatory breast cancers [4, 5], the median overall survival was 69.2 months with a median disease-free survival of 41.9 months.

Therefore we decided to test this AVCF regimen in a neoadjuvant situation for operable and non-metastatic breast tumours; 48 patients were treated with an interval period reduced from 3 to 2 weeks, with good tolerance. To maximise the result, we then treated 80 patients with addition of methotrexate to AVCF.

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PATIENTS AND METHODS

Patients

Between January 1988 and December 1989, 126 patients with an operable breast cancer were treated by induction chemotherapy: 100 tumours were $\geq$ 3 cm in diameter, and 26 tumours were $<$ 3 cm but situated in the central area of the nipple, indicating modified radical mastectomy (MRM).

Before treatment, each patient underwent a complete check up to detect distant metastasis, and had pathological or cytological probe of malignancy, and prognostic factor determination with a Surecut needle (Nycomed Ingenor): SBR (Scarff-Bloom-Richardson) and modified SBR (MSBR) [6], hormonal receptors by radio-immunology, and cell kinetics using flow cytometry with EPICS Coulter S. Patients' characteristics are indicated in Table 1. 2 patients only needed a surgical biopsy to ascertain malignancy.

Most patients were postmenopausal (68 out of 126). Mean age was 53 years (range: 27–78 years). All were fully evaluable for locoregional response after this ambulatory treatment.

As of 30 June 1991, the median follow-up was 30 months.

Initial staging

This comprised complete clinical examination, bilateral mammography and echography, cytological and histological diagnosis, for primary tumour and nodes. Every patient was proven to be devoid of metastasis by chest X-ray, liver echography, bone scintigraphy. Biological assessment comprised blood cell count, electrolytes, alkaline phosphatases and gamma glutamyl transferase, CEA and CA 153.

Table 1. Patients' characteristics

TNM classification (UICC, 1988)	Patient number
T1	8
T2	94
T3	24
N0	65
N1	57
N2	4

26 patients had a tumour situated in the central area of the nipple

SBR grading	Pretreatment (58*)	Post-chemotherapy (66*)
I	5	11
II	40	40
III	13	15

Modified SBR grading	Pretreatment (77*)	Post-chemotherapy (78*)
1	3	1
2	10	22
3	32	26
4	29	21
5	3	8

Hormonal receptors (101*)	
E− P−	62
E− P+	4
E+ P+	26
E+ P−	9
Cell kinetics	
Presence of aneuploid population	55
S phase ≥ 5%	68
Menopausal status	
Premenopausal	58
Menopausal	68
Pathology	
Invasive ductal carcinoma	104
Invasive lobular carcinoma	9
Unspecified (malignant cells only)	13

* Number of patients assessed.

Chemotherapy

Patients received every 3 weeks the same induction chemotherapy with doxorubicin, 30 mg/m^2 on day 1; vincristine 1 mg/m^2 on day 2; cyclophosphamide 300 mg/m^2 and 5-fluorouracil 400 mg/m^2 on days 2–5. When methotrexate was added, patients received 20 mg/m^2 on days 2 and 4.

Assessment of response

We used three different methods: clinical, echographic and mammographic measurements after 3 and 6 cycles, carried out by the same clinician (V.F.).

Clinical and echographic responses were evaluated by the decrease in the sum of the volumes of tumour, and involved nodes and were classified as follows: complete response (CR), partial > 50% (PR), no change (NC). For mammographic response, PR was defined to be ≥ 30% reduction in the main diameter of the X-ray detected opacity.

Local treatment

After 6 cycles, locoregional treatment was scheduled: radiotherapy if a complete clinical response had been obtained; and surgical resection with postoperative radiotherapy in most other cases (Table 2).

MRM was performed in patients with a poor response and no shrinkage of the tumour volume below 3 cm and in patients with multifocal tumour or diffuse tumour (especially with disseminated microcalcifications). Immediate breast reconstruction was discussed with these patients.

RESULTS

Tolerance

In our study, the tolerance was acceptable without major toxicity. Nausea/vomiting were mild (WHO grade I–II in 97 cases). Methotrexate addition resulted in a grade II mucositis for 11 patients. Alopecia was nearly constant, due to doxorubicin: grade III (22 patients), grade IV (103 patients). 6 patients had a moderate peripheral neuropathy, due to vincristine. Febrile aplasia was uncommon, and treatment was generally resumed on day 21, and in some rare cases on day 28.

Response

Overall response rate (CR + PR) after 6 cycles of chemotherapy was 85.6% (clinical), 75.3% (echography), and 58.8% (mammography). Responses were always higher at the 6th cycle than after the 3rd: treatment prolongation was clearly beneficial and the difference was significant (Table 3).

Clinical and mammographical responses were not different in premenopausal vs. menopausal patients, however with a slightly insignificant higher level of CR in premenopausal. Echographic response was better in premenopausal women,

Table 2. Treatment schedule

Induction Chemotherapy: AVCF or AVCFM (6 cycles)

Complete or nearly complete response	Moderate response < 50% or partial response > 50%		No change or progression
↓	↙	↘	↓
Exclusive radiotherapy (41 cases)	Tumourectomy + radiotherapy (64 cases)	Total mastectomy with or without radiotherapy (16 cases)	Preoperative irradiation Modified radical mastectomy (3 cases)

Treatment refusal after chemotherapy = 2 cases.

Table 3. Tumour/node responses obtained after 3 and 6 cycles

Response (%)	Method (3 or 6 cycles)					
	Clinical		Echography		Mammography	
	3	6	3	6	3	6
CR	9.5	36.4	1.2	21.9	5.3	21.5
PR	55.2	49.2	44.6	53.4	23.9	29.3
MR/NC	35.3	14.4	54.2	24.6	70.8	49.1
P, 3 vs. 6 cycles	< 0.0001		< 0.0001		< 0.0001	

but the difference was of borderline significance ($P < 0.06$). The addition of methotrexate did not result in a significantly higher response rate, unless when assessed by echography ($P < 0.05$) (Table 4).

Objective responses were significantly lower (clinical and

Table 4. Tumour/node responses obtained after 6 cycles

Response (%)	Method (6 cycles)		
	Clinical	Echography	Mammography
CR, menopausal	29.4	9.5	14.7
CR, premenopausal	39.6	26.7	25.9
PR, menopausal	54.4	54.8	33.8
PR, premenopausal	39.6	44.4	22.2
Statistical significance between menopausal and premenopausal	NS	$P < 0.06$	NS
CR (80 with MTX*)	37.5	23.4	22.0
CR (46 without MTX*)	28.3	4.3	15.5
PR (80 with MTX*)	43.8	53.1	27.2
PR (46 without MTX*)	54.3	47.8	31.1
P, with and without MTX	NS	< 0.05	NS

* MTX = methotrexate. NS = not significant.

Table 5. Correlation of the objective response rate: with prognostic factors and treatment used; statistical data

Prognostic factor	Number of patients	Statistical question asked	Method of evaluation (*P*)		
			Clinical	Echography	Mammography
Hormonal receptors O+ P+ O− P− O− P+ O+ P−	26 61 4 9	Lower response rate for O+ P+ patients vs. others	< 0.05*	NS*	< 0.01*
Cell cycle Per cent of cells in S phase (threshold = 10)	91	Higher response rate when S phase cells per cent was higher	NS†	NS†	< 0.01†
Cell cycle Presence of an aneuploid cell peak	55	Higher response rate when presence of an aneuploid peak	NS*	NS*	NS*
Cell cycle Presence of an aneuploid cell peak when MTX was added to treatment	46 without MTX, 80 with MTX	Higher response rate when presence of an aneuploid peak in MTX treated patients	< 0.06*	< 0.02*	< 0.01*
SBR grading, pre-treatment	1 = 5 2 = 40 3 = 13	Higher response rate when higher SBR grading	NS*	< 0.05*	NS*
MSBR grading, pre-treatment	1 = 3 2 = 10 3 = 32 4 = 29 5 = 3	Higher response rate when higher modified SBR grading	NS*	NS*	NS*
Dose intensity and response for all drugs	126	Response rate and relative dose intensity	NS‡	NS‡	NS‡
Doxorubicin relative dose intensity	126	Response rate and doxorubicin relative dose	NS‡	NS‡	NS‡

NS = Not significant.
* Kruskall–Wallis H test.
† Mann–Whitney U test.
‡ Rank correlation coefficient of Spearman.
$P < 0.05$ also for pooled results of clinical, mammographic and echographic evaluation.

Table 6. Results of primary medical treatment

Reference	No. of patients	Primary medical treatment	Local treatment	Rate of breast conservation (%)	Locoregional recurrence
10	250	Chemotherapy	Radiotherapy alone in 176 cases	94	13% at 5 years
13	165	Chemotherapy	Conservative surgery in 142 cases	88	2.6% at 1 year
14	134	Chemotherapy	Radiotherapy alone (40 patients) conservative surgery + radiotherapy (40 cases)	63.1	8.3% at 34 months
8	57	Chemotherapy (15 patients) Endocrine therapy (42 patients)	Radiotherapy alone in 2 cases	82	3.5% at 19 months

mammographical methods) in patients that were positive for both oestrogen and progesterone receptors (Table 5).

A positive correlation was observed between S phase percentage in the cell cycle study and mammographic response at the 6th treatment: this response increased with S phase level ($P < 0.01$). When patients were separated into 2 subgroups ($<$ and $\geq$ 10% of cells in S phase) the significance level increased to $P < 0.01$. The presence of an aneuploid cell population did not have a clear influence on the response per se; however, this response was better with AVCFM than with AVCF, when aneuploid cells were present, by clinical ($P < 0.05$), mammographic ($P < 0.01$), and echographic ($P < 0.02$) evaluations. When available, SBR and MSBR compared before and after therapy were identical in 20 out of 32 for SBR grading, and 20 out of 49 for MSBR. In the cases where a difference in grading was observed, no classifiable shift could be determined. The response observed in the three methods of evaluation was correlated with pretherapeutic SBR ($P < 0.05$) and MSBR (NS, tendency only, due to a higher number of classes) but not with postchemotherapy grading. As a correlation between grading and response was found for every evaluation method, a higher level of significance could be observed with a higher number of patients.

Local control

After chemotherapy induction and according to the tumour response, 41 patients received radiotherapy alone, 64 had conservative surgery and 19 MRM, leading to breast conservation in 105 patients (85%). 6 patients had an immediate breast reconstruction.

Histological response

41 patients did not undergo surgery and are not available for pathological post treatment evaluation. In the other patients, 1 complete remission was obtained and 5 had no residual tumour, but only isolated neoplastic cells. These major pathological results amounted to 7% of the resected patients. Conversely 77 had a residual tumour.

Course of disease

Median survival has not yet been reached; until now, we have observed 2 local, 3 local and metastatic, and 9 metastatic failures, of whom 7 have died from their disease. The local recurrence rate has been 3/41 for radiotherapy alone and was observed in irradiated volume. To date no local relapse has been observed in the group submitted to a breast conservative surgery, but 2/19 for MRM.

DISCUSSION

Neoadjuvant chemotherapy in operable breast cancer is a recent concept. Initially used for locally advanced inoperable breast cancer, many studies [7–9] showed an activity of chemotherapy in primary operable breast cancer.

Response is measured mammographically and clinically [10–13]. In our study, objective results were established in every patient by the combination of three methods: clinical, echographic and mammographic evaluation, and were reviewed by the same clinician. This evaluation may be more homogeneous and complete.

With the neoadjuvant treatment used, our results seemed to be satisfactory with a high response rate, similar to other studies [10, 14, 15]. The number of chemotherapy cycles is probably important. The objective tumour regression was evidently greater at the 6th cycle than after 3 courses only (Table 3). Bonadonna *et al.* [13] found an equivalent result with 5 different neoadjuvant regimens after 3 cycles; however, dose intensity may be important, especially for less differentiated tumours. A greater number of courses could also allow us to reach a greater proportion of dividing cells by treating the tumour during a higher number of cell cycles.

Our approach was satisfactory for breast conservation; tumourectomy was possible in our series for about 85% of patients without increase of local recurrences (4.7%), at least until now. However, a longer follow-up will be necessary. Many studies [10, 13, 14] with primary medical treatment found similar rates of breast conservation and locoregional recurrences (Table 6).

Our study showed that neoadjuvant chemotherapy allowed a conservative approach of locoregional treatment in about 85% of the patients, with exclusive radiotherapy or with surgery plus radiotherapy.

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Tamoxifen as Sole Therapy for Primary Breast Cancer in the Elderly Patient

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In a retrospective study the data concerning 40 patients, with primary operable breast cancer were analysed. The mean follow-up of the patient group was 29 months. All patients received tamoxifen only. 17 (43%) reached remission and there was stable disease in 16 (40%). 7 (18%) showed progression, although they have had stable disease for at least 18 months. There were 1 local, 1 distant and 5 local plus distant progressions. 3 patients required salvage mastectomy. The mean progression-free interval was 33 months. Death was attributable to breast carcinoma in only 6 patients (15%). The 3-year survival was 47.2%. We conclude that primary treatment with tamoxifen as a sole therapy is acceptable in operable breast carcinoma for those patients for whom surgery is contraindicated or who refuse surgery.
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INTRODUCTION

LITTLE IS known about the best treatment of operable breast cancer in the elderly patient. In most clinical trials concerning the primary therapy of breast cancer patients of 70 years or older are excluded. It is not clear whether the results of these trials can be extrapolated to older patients. At present the standard treatment for stage I or stage II breast cancer is mastectomy or lumpectomy followed by irradiation. It has been questioned whether elderly patients should always receive the same standard treatment. Just because of age older patients have been treated differently from younger women [1, 2]. There are several reasons to treat the elderly patient less aggressively. Elderly patients are often unfit for surgery because of concomittant diseases which increase the risk of operation. A non-surgical therapy would avoid this risk. It is expected that the natural course of disease is less aggressive and slower in elderly patients than in younger ones because of greater incidence of oestrogen receptor positivity [3–5]. In view of their short life expectancy it is argued that protracting the course of disease by conservative treatment would be sufficient to avoid unacceptable complications.